REMARKS/ARGUMENTS

Status of the Claims

Claims 43 and 48 have been amended to recite that the presently-claimed methods include continuously or repeatedly administering an opioid narcotic analgesic and a tolerance-reducing or dependence-reducing amount of a nontoxic VR1 antagonist of Formula II. Support for the amendments can be found throughout the present specification, for example, see page 8, line 19 through page 10, line 5 of the application as filed.

Now pending are claims 1-6, 25-57 and 59-71. In the Office Action, claims 1-6, 25-42 and 53-57 and 59 were indicated to be withdrawn, and claims 43-52 and 60-71 to be presently under examination.

Reconsideration of the application is requested.

Rejection of claims under 35 USC 102(e)

In the Office Action, claims 43-45 and 48-50 stand rejected under 35 U.S.C. §102(e), as allegedly anticipated by Kyle et al., U.S. Patent No. 6,974,818 (the "Kyle patent") as evidenced by Goodman and Gilman (2001). This rejection is traversed.

(i) Applicants have previously discussed the teachings and deficiencies of the Kyle Patent (and its priority document(s)); see, e.g., Applicants' paper filed March 23, 2009 (which is incorporated herein by reference). Those arguments are reiterated in part herein; Applicants note that the Office Action continues to refer to the Kyle patent in making the rejection, when (as previously explained), the Kyle patent is not an effective reference against the claims presently under examination.

As previously discussed, MPEP 706.02 (f)(1) I (B) states in part: "The 35 U.S.C. 102(e) date of a reference that did not result from, nor claimed the benefit of, an international application is its earliest effective U.S. filing date, taking into consideration any proper benefit claims to prior U.S. applications under 35 U.S.C. 119(e) or 120 **if** the prior application(s) properly supports the subject matter used to make the rejection in compliance with 35 U.S.C. 112, first paragraph" (emphasis added). MPEP 2136.03(III) reiterates this requirement.

Therefore, an issued patent can be applied as a reference under 35 U.S.C. 102(e) only if the utility application, or one or more of the priority applications, was filed before the invention of the present claims by the present Applicants.

Applicants contend that the present claims are entitled to at least the filing date of the priority application USSN 60/433,363, filed December 13, 2002, to which the present application claims priority. The Kyle utility application (USSN 10/374,863) was filed on February 27, 2003, and thus was not filed "before the invention by the [present] applicant for patent".[1] Therefore, the disclosure of the Kyle utility application (USSN 10/374,863) and the Kyle patent as issued cannot be used in a rejection under 35 U.S.C. 102(e) unless such disclosure is present in an application to which the Kyle utility application properly claims priority. Cf. Ex parte Yamaguchi, 88 USPQ2d 1606 (Bd. Pat. App. & Int. 2008).

It follows that the discussion in the Office Action of the disclosure of the Kyle patent (see, e.g., the Office Action at page 3, last paragraph) is irrelevant and improper as the basis for a rejection under 35 U.S.C. 102(e) unless that disclosure is found in one of the Kyle priority applications. The rejection of the present claims based on the asserted portions of the Kyle patent cannot stand.

Furthermore, as previously discussed, Applicants contend that the disclosure of the Kyle priority application(s) do not anticipate the pending claims. As previously mentioned (see the previous responses April 8, 2008, and March 23, 2009), the bare recitation of "an addictive disorder" in the Kyle priority application can hardly be said to describe or enable methods for inhibiting the development of tolerance to or dependence on a narcotic analgesic, as recited in the pending claims under examination. To the extent that the Kyle priority application does mention "that the compounds of the [Kyle] invention are used for the treatment of addictive disorders," as stated in the Office Action, Applicants submit that the Kyle priority application does not enable such use. Notwithstanding the unsupported statement in the Office Action that "the [Kyle] priority document teaches that Thiadiazolepiperazine compounds treat an addictive disorder [and treatment] of addictive disorders encompasses treating

tolerance", Applicants submit that in fact the cited portions of the Kyle priority document do not properly support the subject matter used to make the rejection in compliance with 35 U.S.C. 112, first paragraph.

Applicants note that the pending claims recite that the presently-claimed methods include continuously or repeatedly administering an opioid narcotic analgesic and a tolerance-reducing or dependence-reducing amount of a nontoxic VR1 antagonist. The Kyle priority application 60/411,084 does not teach or suggest continuous or repeated administration of both an opioid narcotic analgesic and a tolerance-reducing or dependence-reducing amount of a nontoxic VR1 antagonist.

The Office Action states that

> Goodman and Gilman's teaches that the development of tolerance with repeated use is a characteristic feature of all the opioid drugs. Therefore it is inherent that a patient will be continuously and repeatedly administering the opioid narcotic analgesic and it would inherently follow that a patient will administer a treatment to block the ability to develop tolerance with the opioid analgesic.

Office Action at page 4.

This statement is not understood. While an opioid drug can be administered continuously or repeatedly, there is nothing "inherent" in the cited references about the administration of a (i) an opioid narcotic analgesic; and (ii) a tolerance-reducing (or dependence-reducing) amount of a nontoxic VR1 antagonist, as required by the pending claims.

(ii) In addition to the foregoing reasons, Applicants contend that the Kyle patent cannot anticipate the pending claims, which are directed to methods in which, *inter alia*, a tolerance-reducing (or dependence-reducing) amount of a nontoxic VR1 antagonist of the formula recited in claims 43 and 48 (Formula II) is administered to a patient. Such VR1 antagonists are not taught or suggested by the Kyle patent. The Kyle patent simply cannot anticipate the pending claims.

Reconsideration and withdrawal of the rejection is proper and the same is requested.

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[1] Solely for purposes of this discussion, the filing date of the priority application USSN 60/433,363 is mentioned as the latest date of invention of the present claims. Applicants reserve the right to assert an earlier date of invention.

Rejection of claims under 35 U.S.C. §103(a)

In the Office Action (at pages 4-5), claims 46-47, 51-52, and 60-71 stand rejected under 35 U.S.C. §103(a), as allegedly unpatentable over Kyle et al., U.S. Patent No. 6,974,818, in view of Bakthavatchalam et al., U.S. Patent No. 6,723,730 (the "Bakthavatchalam patent"). This rejection is traversed.

As noted above, the Kyle patent simply does not teach (for purposes of 35 U.S.C. 102(e)) what the Office Action asserts that it teaches. As also discussed above, the Kyle priority application(s) do not teach or suggest methods for inhibiting the development of tolerance to or dependence on a narcotic analgesic, as recited in the pending claims. Moreover, the Kyle patent does not teach or suggest continuous or repeated administration of both an opioid narcotic analgesic and a tolerance-reducing or dependence-reducing amount of a nontoxic VR1 antagonist, let alone administration of an opioid narcotic analgesic and a tolerance-reducing or dependence-reducing amount of a nontoxic VR1 antagonist of Formula II as recited in the pending claims.

Applicants also disagree with the statement that

> Kyle et al. does teach that the VR1 antagonist of the invention can act synergistically with the therapeutic agent . . . Therefore, it would be obvious to vary and/or optimize the amount of the opioid narcotic analgesic provided in the composition, according to the guidance provided by Kyle et al., to provide a composition having the desired properties . . . to provide analgesia while not developing tolerance.

Applicants again note that the teachings of the Kyle patent are not available for citation as prior art under 35 U.S.C. 102(e)/103(a). To the extent that the arguments in the Office Action are taken to refer to the Kyle priority application 60/411,084, Applicants note that the Kyle priority application does not teach that VR1 antagonists in general are useful in the treatment of addictive disorders. Instead, the Kyle priority application discloses – e.g., at page 20, lines 15 – 20 - that "[e]xamples of conditions that are treatable or preventable by inhibiting mGluR1 function include, but are not limited to . . . pain, UI, an addictive disorder . . . [a]ccordingly, the Thiadiazolepiperazine Compounds are useful for treating or preventing pain, UI, an addictive disorder . . . " (emphasis added).

In contrast, the Kyle priority application states (at page 19, lines 21-22) that the thiadiazolylpiperazine compounds disclosed therein are believed to be VR1 antagonists, and (at page 19, lines 23-31) that methods for inhibiting VR1 function in a cell can be used to "treat[ ] or prevent[ ] . . . pain, urinary incontinence (UI), an ulcer, inflammatory-bowel disease (IBD), and irritable-bowel syndrome (IBS)." Applicants note that the Kyle priority application does not state that VR1 antagonists generally can be used for treatment of addictive disorders (or, more particularly, that VR1 antagonists in general are useful for inhibiting the development of tolerance to a narcotic analgesic in a patient, or for inhibiting the development of dependence on a narcotic analgesic in a patient, as recited by claims 43, 48, and their respective dependent claims). At most, the teachings of Kyle would be limited to the compounds disclosed therein.

The Office Action does not contend that the Bakthavatchalam patent can supply these omitted teachings. The Bakthavatchalam patent does not teach or suggest continuous or repeated administration of both an opioid narcotic analgesic and a tolerance-reducing or dependence-reducing amount of a nontoxic VR1 antagonist. Even if the Kyle reference is taken to teach that a specific class of compounds disclosed therein can be used together with opioids for the treatment of pain, Applicants respectfully submit that, in view of the teaching of the Kyle priority application that treatment of pain is associated with inhibition of mGluR1 function (not VR1 function), one of ordinary skill in the art would not be motivated to combine the teachings of Kyle with any reference disclosing VR1 modulators, and would in any event not have a reasonable expectation of success in making such a combination. Therefore, the claimed methods for the inhibition of the development of tolerance to a narcotic analgesic in a patient, or for inhibiting the development of dependence on a narcotic analgesic in a patient, as recited by claims 43, 48, and their respective dependent claims, are not rendered unpatentable by Kyle or Bakthavatchalam, whether taken alone or in combination. Applicants contend the rejection over the Kyle patent in view of the Bakthavatchalam patent is therefore improper and should be withdrawn.

Reconsideration and withdrawal of the rejection is proper and the same is requested.

CONCLUSION

For at least the foregoing reasons, Applicants contend that the rejections of record should be withdrawn, and that the present application is in condition for allowance. Early and favorable consideration of the application is earnestly solicited.

Applicants conditionally petition for any extension of time required for consideration of this paper. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 60004 (72021).

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Respectfully submitted,

By: /Mark D. Russett/
Mark D. Russett, Registration No.: 41,281
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 239-0100
Attorneys/Agents For Applicants